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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,683	05/20/2004	Jean-Jacques Berthelon	MERCK 2358	7804

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EXAMINER

COLEMAN, BRENDA LIBBY

ART UNIT	PAPER NUMBER
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1624

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/20/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.	Applicant(s)	
10/019,683	BERTHELON ET AL.	
Examiner	Art Unit	
Brenda L. Coleman	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 October 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) 9-11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 and 12-20 is/are rejected.
- 7) ☒ Claim(s) 8 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>8/11/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-20 are pending in the application.

Election/Restrictions

1. Applicant's election with traverse of Group II in the reply filed on October 23, 2006 is acknowledged. The traversal is on the ground(s) that the PTO has not established that it would pose an undue burden to examine the full scope of the application. This is not found persuasive because first a compound containing a bicyclic, tricyclic and tetracyclic ring system are structurally dissimilar compounds, which are classified in various subclasses under class 540 with respect to the number and type of additional heterocyclic rings.

(1) Note MPEP 2173.05(h) "where a Markush expression is applied only to a portion of a chemical compound, the propriety of the grouping is determined by a consideration of the compound as a whole, and does not depend on there being a community of properties in the members of the Markush expression. Therefore, what should be considered for patentable distinctness is the compound as a whole. Would a whole compound where the formula is a benzodiazepine be patentably distinct from a whole compound where the benzodiazepine is further fused forming a tricyclic or tetracyclic? If a reference for one would not be a reference for the other, then restriction is considered proper. Community of properties is not enough to keep benzodiazepine, thiazolo[2,3-b]-1,3-benzodiazepine, etc. in the same Markush claim, where the Markush expression is applied only to a portion of a chemical compound. It is the compound as

Art Unit: 1624

a whole benzodiazepine vs. thiazolo[2,3-b]-1,3-benzodiazepine, etc., that must be considered for patentable distinctness.

Thus, separate searches in the literature would be required. However, should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

(2) The degree of burden on the examiner is high. The class/subclass search on the elected invention where the compounds of formula I contains a tricyclic ring system ring as shown in the applicants' elected species would be as follows: class 514, subclass 220 and class 540, subclasses 497 and 498, which involved 1027 US patents. The classes and subclass mentioned above represent only the degree of burden within the U.S. Patent Classification System, this does not include the search required in the prior art of journal articles and foreign patents.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 9-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 23, 2006.

Priority

3. Any non-provisional application claiming the benefit of one or more prior filed copending nonprovisional applications or international applications designating the United States of America must contain or be amended to contain in the first sentence of the specification following the title a reference to each such prior application, identifying it by application number (consisting of the series code and serial number) or international application number and international filing date and indicating the relationship of the applications. Cross-references to other related applications may be made when appropriate.

"This application is a national stage entry under 35 U.S.C. § 371 of PCT/EP00/06230, filed July 4, 2000." is suggested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the

Art Unit: 1624

predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The nature of the invention in the instant case, has claims which embrace substituted tricyclic ring systems containing the 1,3-benzodiazepine core of formula I. The instant compounds of the formula wherein the R_4 and R_5 are taken together to form a group $-CR_6=CR_7-$ in which CR_6 is linked to X.

HOW TO USE: Claims 18 and 19 are to a method of preventing or treating dyslipidaemia, atherosclerosis and diabetes. Any evidence presented must be commensurate in scope with the claims and must clearly demonstrate the effectiveness of the claimed compounds. The scope of the method claims is not adequately enabled solely based on its capability of reducing the secretion of apo CIII. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. It is difficult to treat many of the disorders claimed herein. Instant claim language embraces disorders not only for treatment but **prevention**, which is not remotely enabled. It is presumed in the prevention of the diseases and/or disorders claimed herein there is a way of identifying those people who may develop dyslipidaemia, atherosclerosis and diabetes. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disorders claimed herein.

No screening protocol(s) are ever described. Thus, no evidence of in vitro effectiveness is seen in the specification for one of the instantly claimed fused 1,3-benzodiazepine compounds. In general, pharmacological activity is a very unpredictable area. In cases involving physiological activity "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Since this case involves unpredictable in-vivo physiological activities, the scope of the enablement given in the disclosure presented here was found to be low.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claims 1-7 and 12-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

- a) Claims 1, 15, 16, 20 and claims dependent thereon are vague and indefinite in that it is not known what is meant by "Derivative" which implies more than what is positively recited.
- b) Claim 1 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the definition of R_5 wherein R_5 includes "the assembly".
- c) Claim 1 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the definition of Z, which is not stated in the form of a proper Markush grouping.

Art Unit: 1624

- d) Claim 1 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the definition of St where there are two different definitions.
- e) Claim 1 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the definition of R^o wherein R^o includes "the assembly".
- f) Claim 1 and claims dependent thereon are vague and indefinite in that it is not known what is meant by Su as defined above in line 31 on page 88.
- g) Claim 2 is vague and indefinite in that it is not known what is meant by the definition of R₄ and R₅ together form -CR₆=CR₇, which is missing a point of attachment.
- h) Claim 6 recites the limitation "aromatic" in the definition of Z. There is insufficient antecedent basis for this limitation in the claim.
- i) Claim 6 recites the limitation "(C₆-C₁₀)aryl (optionally substituted with halogen, optionally halogenated (C₁-C₆)alkyl, optionally halogenated (C₁-C₆)alkoxy or nitro)" in the definition of the substituents on the aryl and heteroaryl portions of Z. There is insufficient antecedent basis for this limitation in the claim.
- j) Claim 6 recites the limitation "(C₆-C₁₀)aryl (this radical optionally being substituted with halogen, optionally halogenated (C₁-C₆)alkyl, (C₁-C₆)alkoxy or nitro)" in the definition of the substituents on the aryl and heteroaryl portions of R₇. There is insufficient antecedent basis for this limitation in the claim.

Art Unit: 1624

k) Claim 15 is vague and indefinite in that it is not known what is meant by the definition of R₄ and R₅ together form a -CR₆=CR₇- group, where there is no R₄ or R₅ in formula V.

l) A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 16 recites the broad recitation between 50 and 150°C, and the claim also recites between 60 and 100°C, which is the narrower statement of the range/limitation.

m) Claim 19 provides for the use of the compounds of formula I, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is

Art Unit: 1624

indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claim 19 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-7 and 16-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Gerand et al., FR 2 550 199. Gerand teaches the compounds, compositions, process of preparing and method of use of the compounds of formula I where n is 0, 1 or 2; R₁ is methoxy, propoxy, fluoro or chloro; R₂ is hydrogen, phenyl, 3-chlorophenyl, 3-methoxyphenyl, 4-methylphenyl, 4-chlorophenyl, 4-methoxyphenyl, 3-methylphenyl or

Art Unit: 1624

2-methoxyphenyl; R₃ is hydrogen; X is NT; R₄ and R₅ together form a group -CR₆=CR₇- where R₆ is hydrogen, methyl or phenyl; and R₇ is OH as set forth in examples 1-14, 16, 19-22, 25, 26, 28-30 and 32.

Claim Objections

8. Claim 8 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims **and limited to the elected invention**. None of the prior art of record or a search in the pertinent art area teaches or fairly suggests the substituted species as claimed herein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda L. Coleman whose telephone number is 571-272-0665. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic

Art Unit: 1624

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

A handwritten signature in cursive script that reads "Brenda Coleman". The signature is written in black ink and is positioned above the printed name and title.

Brenda L. Coleman
Primary Examiner Art Unit 1624
December 18, 2006